

Commentary

Open Access

Small non-coding RNAs, mammalian cells, and viruses: regulatory interactions?

Man Lung Yeung¹, Monsef Benkirane² and Kuan-Teh Jeang^{*1}

Address: ¹Molecular Virology Section, Laboratory of Molecular Microbiology National Institute of Allergy and Infectious Diseases, National Institutes of Health Bethesda, Maryland 20892-0460, USA and ²Insitute de Genetique Humaine, Montpellier, France

Email: Man Lung Yeung - yeungm@mail.nih.gov; Monsef Benkirane - Monsef.BenKirane@igh.cnrs.fr; Kuan-Teh Jeang* - KJEANG@niaid.nih.gov

* Corresponding author

Published: 15 October 2007

Received: 10 October 2007

Retrovirology 2007, **4**:74 doi:10.1186/1742-4690-4-74

Accepted: 15 October 2007

This article is available from: <http://www.retrovirology.com/content/4/1/74>

© 2007 Yeung et al; licensee BioMed Central Ltd.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Recent findings suggest that mammalian cells can use small non-coding RNAs (ncRNA) to regulate physiological viral infections. Here, we comment on several lines of evidence that support this concept. We discuss how viruses may in turn protect, suppress, evade, modulate, or adapt to the host cell's ncRNA regulatory schema.

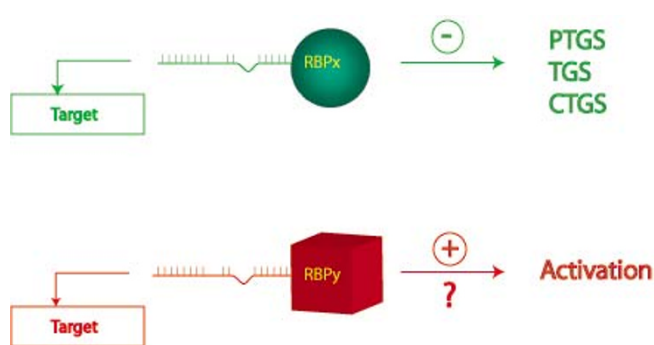
Small RNAs: interference and activation?

Plant and animal genomes have thousands of genes that encode non-protein-coding (nc) RNAs. While recent attention has focused significantly on small interfering RNAs (siRNAs) and micro RNAs (miRNAs), ncRNAs also include rRNA, tRNA, small nuclear (sn) RNA, small nucleolar (sno) RNAs, and some of the lesser-known RNAs such as vault RNAs, Y RNAs, rasi-RNAs and piRNAs [reviewed in [1]]. It is now recognized that only 2% of the human genome encodes for protein-coding RNAs while 60 to 70% of our DNA is transcribed into ncRNAs [2,3]. Hence, despite accumulating research on siRNA, miRNA and piRNA, we are likely at the tip of the iceberg in our understanding about functions and regulatory roles served by ncRNAs in cellular metabolism, pathogenesis and host-pathogen interaction.

A key biological process served by small ncRNAs is a phenomenon termed RNA interference (RNAi). Recent reviews have reprised the discovery of RNAi and summarized the current state of knowledge about this process [4,5]. In brief, a central tenet of RNAi posits that small guide RNAs recruit, in a sequence-complementary man-

ner, a multi-protein complex composed in part of RNA-binding proteins to RNA targets. This large multi-protein RNAi complex has been shown to include members of the Argonaute ribonuclease III protein family; and depending on biological context, the complex has been found to effect post-transcriptional gene silencing (PTGS), transcriptional gene silencing (TGS), and/or co-transcriptional gene silencing (CTGS) (Fig. 1, top).

Conventional wisdom suggests that biological processes are balanced by two principles, yin and yang, which oppose one another in their actions to confer equilibrium. For example, the cell-proliferative effects of oncogenes are countered by commensurate provocations of cellular senescence and apoptosis [6-8]. Moreover, frequently, potent transcriptional activators are also equally strong repressors [9,10]. Indeed, recent developments raise that the yin (negative) of RNAi may be shadowed by a yang (positive). Thus, some cellular [11-14] and viral [15] studies now suggest that a rarely-glimpsed face of "RNAi" may visualize activation rather than repression. Verily, RNA sequence-mediated positive regulation could exist more prevalently than currently acknowledged since, in princi-

**Figure 1**

Schematic representations of positive and negative regulation mediated through ncRNA-guide sequences. RBPx is to illustrate a negative multi-RNA-binding protein regulatory complex that is tagged by a ncRNA-guide and recruited based on sequence-complementarity to target; while RBPγ is to represent a theoretical positive multi-RNA-binding protein complex. PTGS, post-transcriptional gene silencing; TGS, transcriptional gene silencing; CTGS, co-transcriptional gene silencing. Currently, while there are many examples of RBPx, there is yet little published evidence for RBPγ.

ple, there is no reason why other RNA-binding proteins different from Argonaute-related members cannot be similarly tagged and guided by ncRNAs (Figure 1, bottom).

Mammalian cells, viruses and small ncRNAs

Biological studies on mammalian viruses have illuminated aspects of gene regulation by small non-coding RNAs and their RNA-binding proteins. Early results from the HIV-1 TAR RNA and its binding protein Tat framed a platform for how a small non-coding RNA and a viral RNA-binding protein cooperate to up modulate gene expression [16,17]. Indeed, although unrecognized at the time, the first human cellular protein identified to bind TAR RNA, TRBP [18,19] presaged a clue to the mechanistic process of RNAi. Hence, fourteen years after the initial characterization of its binding to TAR, TRBP was revealed as a crucial component of the mammalian miRNA processing machinery [20-22]. Consistent with TRBP's role in miRNA-processing, a recent report demonstrated that TAR RNA in human cells is engaged by TRBP and processed by the RNase III Dicer protein into a miRNA guide [23].

The above sequence of events notwithstanding and although the RNAi machinery is preserved intact in mammalian cells and mammalian RNAi machinery can be instructed to target invading viruses in therapeutic settings, there is a school of thought that mammals do not use ncRNA/RNAi to regulate viral infections [24]. This view is partly rationalized by the argument that mammals

have a surfeit of other means to defeat effectively viral pathologies; thus an intact mammalian RNAi machinery is not needed, and cells have extinguished this mechanism as it applies to viral infection [24]. Confoundingly, that annually 3 million human deaths arise from HIV-infection alone [25] and ~20% of all human cancers are caused by viral infections [26] indicate that mammalian defenses are not nearly so replete that effective antiviral pathway(s) should become extinct.

Recent experimental findings are, in fact, consistent with physiological use by mammalian cells of small ncRNA/RNAi to regulate viruses. First, three studies have converged to illustrate that small ncRNAs (siRNAs and piRNAs) are used in human and mouse cells to suppress the replication of endogenous retroviruses (i.e. retrotransposons) [27-29]. Second, bioinformatics and experimental results persuasively imply that mammalian viruses including HIV-1 are targeted by discrete human miRNAs [30-34]. Third, repression of mammalian Dicer enzyme was found to up regulate cellular replication of HIV-1 and vesicular stomatitis virus (VSV) [35-37]. One straightforward interpretation of the latter finding, which does not exclude others, is that the unrepressed mammalian Dicer-RNAi pathway normally acts to moderate HIV-1 and VSV replication. Finally, a KSHV viral miRNA (miR-K12-11) was identified as a viral orthologue of human miR-155 [38]. To the extent that miR-K12-11 targets KSHV- and cellular- sequences, then cellular miR-155 can be reasoned to act upon the same KSHV-sequence regulated by miR-K12-11. Indeed, pending the clarification of additional details, extant observations are consistent with the employment of ncRNAs by mammalian viruses to regulate viral functions, by mammalian cells to regulate cellular functions, and by mammalian viruses to regulate cellular functions, and by mammalian cells to regulate viral functions (Figure 2).

Viral responses?

If cells restrict viruses with non-coding RNAs, do viruses respond with countermeasures? In principle, viral counter stratagems could include a) protection from restriction, b) suppression of restriction; c) evasion from restriction; d) modulation of restriction profiles, and e) adaptation to restriction.

Protection

Experimental findings suggest the existence for mammalian viruses of each of the above five mechanisms. Regarding protection, Berkhout and colleagues have reported that RNA genomes can be physiologically shielded from RNAi in a privileged format [39]. Nevertheless, this protection cannot prevail for unpackaged viral genomes or for transcribed viral mRNAs. Accordingly, viral mechanism(s) for RNAi-blunting or -suppression might be required in unprotected settings.

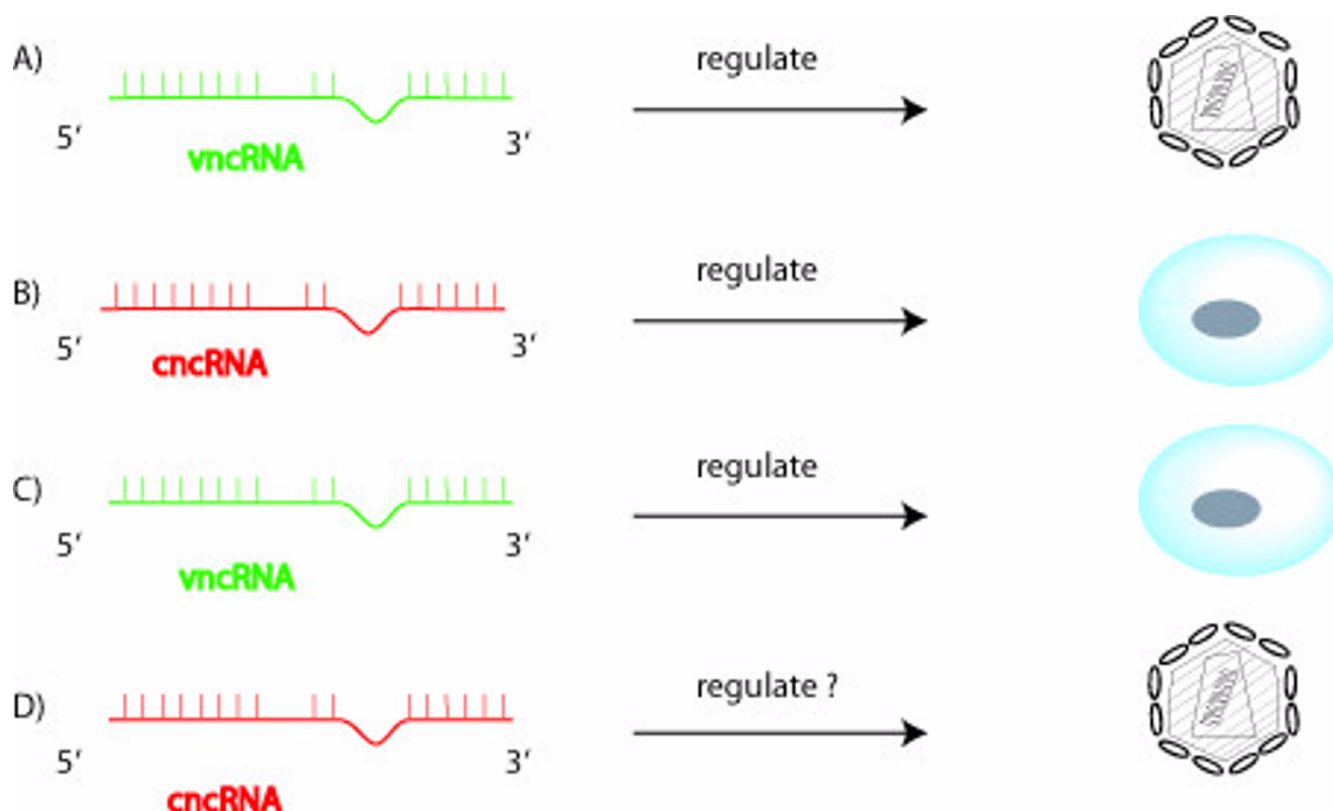


Figure 2

Four different ways for viral (v) ncRNAs and cellular (c) ncRNAs to interact in mammalian cells. A) shows vncRNA regulating virus; B) shows cncRNA regulating cells; C) shows vncRNA regulating cells; D) illustrates cncRNA regulating virus. Experimental evidence compatible with each of these four pathways exists in the published literature.

Suppression

Indeed, viruses appear to possess at least two means to suppress RNAi. First, virus-encoded RNA-binding proteins partly serve an RNAi-neutralization function. This mechanism while well-accepted for viruses in lower eukaryotic cells [40] has been debated for mammals. Relevant to HIV-1, two studies have attributed RNAi-suppressive activity to the arginine-rich RNA-binding Tat protein [41,42], while a third study has questioned this concept [43]. Interestingly, the interpreted absence of Tat-associated RNAi-suppression in the latter study is complicated by high non-specific transcriptional activation of TAR-less cellular promoters by Tat, a finding inconsistent with the known specificity of Tat for TAR-RNA [44-46]. Second, in a separate way, mammalian viruses suppress RNAi by synthesizing small viral RNA decoys that competitively occupy RNAi machinery, preventing the processing of authentic RNAi precursors [47-49]. Because stringent global suppression of RNAi is likely incompatible with the viability of mammalian cells [50], virus-mediated RNAi-suppression is likely to be physiologically modest and localized in scope. This could explain difficulties in visu-

alizing suppressive activities in non-viral transfection-based over expression assays.

Evasion

If protection or suppression fails, viruses can evade sequence-complementarity-driven RNAi through mutations. Highly mutable viruses like HIV-1 are proficient at sequence- or secondary structure- changes [51,52]. Experimental findings of rapid HIV-1 mutation under artificial siRNA-pressure do not, however, address whether ncRNA-based selection against HIV-1 exists physiologically in human cells. Here, supportive data are difficult to accumulate because by definition effective evasion (from e.g. miRNAs) means loss of evidence for base complementarity in viral genomes (to miRNAs). Hence, viruses with no human miRNA-footprints may actually be viruses that experience the strongest miRNA- selection. In a setting where an absence of finding may be indicative of evasion, how might one collect clues? An answer may reside with searching for human miRNA-target sites in viral genomes containing tell-tale mismatches. For example, rare HIV-1 sequence which appears to be targeted by human miRNAs

(see Figure 3, an HIV pNL4-3 "target" of human miR-326) carries a hallmark change near the miR-seed sequence partly consistent with APOBEC (deoxycytidine deaminase) -mediated G to A mutation. In this example, one could change the putatively escaped "A" back to a "G" in the HIV genome, and test if the original "non-escaped" HIV-1 is subject to vigorous miR-326-selection. Such experimental design could provide findings supportive of a hypothesis that current HIV-1 RNA sequences are continually shaped and maintained by ambient RNAi pressure.

Modulation and adaptation

Failing protection, suppression, and evasion from miRNAs, viruses may modulate the cell's miRNA expression profile [35,53], or viruses may ultimately adapt miRNA-restriction to benefit viral replication [15]. In the former setting, RNA-binding proteins such as Tat which act in the nucleus as well as affect cytoplasmic events via binding to tubulin [54-56] could significantly remodel cellular miRNA profiles [53]. In the latter scenario, human hepatitis C virus is currently the one rare example compatible with an adaptation paradigm [15]. As we learn more about miRNA -targets and -biology, better understandings of setting-specific negative versus positive modulations and adaptations will likely emerge.

Perspectives and Predictions

We have outlined in brief two views on virus- cell ncRNA interaction in mammals. The first view embraces a null hypothesis --- virus-cell ncRNA interactions exist in lower eukaryotes but not physiologically in mammals [24]. While this view may be correct, several lines of evidence discussed here point against its limitations. A second view

is that the RNAi machinery exists in mammalian cells not just for artificial siRNA-exploits but as a physiological mechanism used by cells and viruses to regulate viral and cellular functions (Figure 2). Subsumed within this view is the thesis that RNAi is a part of the armamentarium used by mammalian cells to regulate, perhaps positively and negatively in context-specific fashion, the replication of endogenous and exogenous viruses. We anticipate that more time and further investigation will be needed to validate the accuracy of the one or the other view point.

If small ncRNAs are used in mammalian cells to regulate cellular and viral functions, then one could venture several predictions. First, many more (cellular and viral) RNA-binding proteins that adapt small RNAs to mediate both negative and positive gene regulation will be revealed. Second, mammalian viruses will be shown to encode a variety of ncRNAs that have regulatory roles. Some future examples might mirror the HTLV-1 regulatory HBZ ncRNA [57]; others may emerge from the processing of antisense HIV-1 and HTLV-1 transcripts [58-60]; and even others may behave like TAR or RRE. Third, additional viral RNA-binding proteins (perhaps Rev and Rex) will be shown to have setting-specific RNAi- modulatory properties, and many viruses will be found to extensively reshape cellular miRNA expression profiles.

Since its first description a relatively short period of time ago, 9868 papers have already been published on RNAi (data from Pubmed search using the term, RNAi). An additional prediction (which will almost certainly be correct) is that RNA-guided gene regulation will continue to hold many exciting and unexpected scientific findings which will be published profusely in the coming years.



Figure 3

A potential foot print of an HIV-1 escape mutation from human miRNA-mediated selection. The HIV-1 sequence (bottom strand) shown in this figure is from the LTR of pNL4-3. Good base pairing of this sequence with human miR-326 (top strand) is shown (current); however, an even better base pairing (original?) is inferred if a putative APOBEC -mediated "G" to "A" change is corrected.

Acknowledgements

We thank Dr. Shu-Yun Le for ongoing assistance with bioinformatics, Drs. Ben Berkhout and Fatah Kashanchi for critical readings, and Blair Clemente for help with artwork.

References

- Backofen R, Bernhart SH, Flamm C, Fried C, Fritzsche G, Hackermüller J, Hertel J, Hofacker IL, Missal K, Mosig A, Prohaska SJ, Rose D, Stadler PF, Tanzer A, Washietl S, Will S: **RNAs everywhere: genome-wide annotation of structured RNAs.** *J Exp Zool B Mol Dev Evol* 2007, **308**:1-25.
- Mattick JS, Makunin IV: **Non-coding RNA.** *Hum Mol Genet* 2006, **15 Spec No 1**:R17-R29.
- Washietl S, Hofacker IL, Lukasser M, Huttenhofer A, Stadler PF: **Mapping of conserved RNA secondary structures predicts thousands of functional noncoding RNAs in the human genome.** *Nat Biotechnol* 2005, **23**:1383-1390.
- Rana TM: **Illuminating the silence: understanding the structure and function of small RNAs.** *Nature Reviews Molecular Cell Biology* 2007, **8**:23-36.
- Berkhout B, Jeang KT: **RISCy business: MicroRNAs, pathogenesis, and viruses.** *J Biol Chem* 2007, **282**:26641-26645.
- Shaulian E, Karin M: **AP-1 as a regulator of cell life and death.** *Nat Cell Biol* 2002, **4**:E131-E136.
- Mallette FA, Ferbeyre G: **The DNA damage signaling pathway connects oncogenic stress to cellular senescence.** *Cell Cycle* 2007, **6**:1831-1836.
- Matsuoka M, Jeang KT: **Human T-cell leukaemia virus type I (HTLV-I) infectivity and cellular transformation.** *Nat Rev Cancer* 2007, **7**:270-280.
- Xiao L, Rao JN, Zou T, Liu L, Marasa BS, Chen J, Turner DJ, Passaniti A, Wang JY: **Induced JunD in intestinal epithelial cells represses CDK4 transcription through its proximal promoter region following polyamine depletion.** *Biochem J* 2007, **403**:573-581.
- Jeang KT, Widen SG, Semmes OJ, Wilson SH: **HTLV-I trans-activator protein, tax, is a trans-repressor of the human beta-polymerase gene.** *Science* 1990, **247**:1082-1084.
- Li LC, Okino ST, Zhao H, Pookot D, Place RF, Urakami S, Enokida H, Dahiya R: **Small dsRNAs induce transcriptional activation in human cells.** *Proc Natl Acad Sci U S A* 2006, **103**:17337-17342.
- Bhattacharyya SN, Habermacher R, Martine U, Closs EI, Filipowicz W: **Relief of microRNA-mediated translational repression in human cells subjected to stress.** *Cell* 2006, **125**:1111-1124.
- Vasudevan S, Steitz JA: **AU-rich-element-mediated upregulation of translation by FXR1 and Argonaute 2.** *Cell* 2007, **128**:1105-1118.
- Leung AK, Sharp PA: **microRNAs: a safeguard against turmoil?** *Cell* 2007, **130**:581-585.
- Jopling CL, Yi MK, Lancaster AM, Lemon SM, Sarnow P: **Modulation of hepatitis C virus RNA abundance by a liver-specific microRNA.** *Science* 2005, **309**:1577-1581.
- Berkhout B, Silverman RH, Jeang KT: **Tat trans-activates the human immunodeficiency virus through a nascent RNA target.** *Cell* 1989, **59**:273-282.
- Dingwall C, Ernberg I, Gait MJ, Green SM, Heaphy S, Karn J, Lowe AD, Singh M, Skinner MA, Valerio R: **Human immunodeficiency virus I tat protein binds trans-activation-responsive region (TAR) RNA in vitro.** *Proc Natl Acad Sci U S A* 1989, **86**:6925-6929.
- Gatignol A, Buckler-White A, Berkhout B, Jeang KT: **Characterization of a human TAR RNA-binding protein that activates the HIV-1 LTR.** *Science* 1991, **251**:1597-1600.
- Gatignol A, Laine S, Clerius G: **Dual role of TRBP in HIV replication and RNA interference: viral diversion of a cellular pathway or evasion from antiviral immunity?** *Retrovirology* 2005, **2**:65.
- Forstemann K, Tomari Y, Du T, Vagin VV, Denli AM, Bratu DP, Klattehoff C, Theurkauf WE, Zamore PD: **Normal microRNA maturation and germ-line stem cell maintenance requires Loquacious, a double-stranded RNA-binding domain protein.** *PLoS Biol* 2005, **3**:e236.
- Chendrimada TP, Gregory RI, Kumaraswamy E, Norman J, Cooch N, Nishikura K, Shiekhattar R: **TRBP recruits the Dicer complex to Ago2 for microRNA processing and gene silencing.** *Nature* 2005, **436**:740-744.
- Haase AD, Jaskiewicz L, Zhang H, Laine S, Sack R, Gatignol A, Filipowicz W: **TRBP, a regulator of cellular PKR and HIV-1 virus expression, interacts with Dicer and functions in RNA silencing.** *EMBO Rep* 2005, **6**:961-967.
- Klase Z, Kale P, Winograd R, Gupta MV, Heydarian M, Berro R, McCaffrey T, Kashanchi F: **HIV-1 TAR element is processed by Dicer to yield a viral micro-RNA involved in chromatin remodeling of the viral LTR.** *BMC Mol Biol* 2007, **8**:63.
- Cullen BR: **Is RNA interference involved in intrinsic antiviral immunity in mammals?** *Nat Immunol* 2006, **7**:563-567.
- UNAIDS: **The Joint United Nations Programme on HIV/AIDS** 2007 [http://www.unaids.org].
- Cuzick J: **Viruses and cancer.** *J Epidemiol Biostat* 2000, **5**:143-152.
- Yang N, Kazazian HH Jr.: **LI retrotransposition is suppressed by endogenously encoded small interfering RNAs in human cultured cells.** *Nat Struct Mol Biol* 2006, **13**:763-771.
- Watanabe T, Takeda A, Tsukiyama T, Mise K, Okuno T, Sasaki H, Minami N, Imai H: **Identification and characterization of two novel classes of small RNAs in the mouse germline: retrotransposon-derived siRNAs in oocytes and germline small RNAs in testes.** *Genes Dev* 2006, **20**:1732-1743.
- Carmell MA, Girard A, van de Kant HJ, Bourchis D, Bestor TH, de Rooij DG, Hannon GJ: **MIWI2 is essential for spermatogenesis and repression of transposons in the mouse male germline.** *Dev Cell* 2007, **12**:503-514.
- Hariharan M, Scaria V, Pillai B, Brahmachari SK: **Targets for human encoded microRNAs in HIV genes.** *Biochem Biophys Res Commun* 2005, **337**:1214-1218.
- Scaria V, Hariharan M, Maiti S, Pillai B, Brahmachari SK: **Host-virus interaction: a new role for microRNAs.** *Retrovirology* 2006, **3**:68.
- Huang J, Wang F, Argyris E, Chen K, Liang Z, Tian H, Huang W, Squires K, Verlingieri G, Zhang H: **Cellular microRNAs contribute to HIV-1 latency in resting primary CD4(+) T lymphocytes.** *Nat Med* 2007, **13**:1241-1247.
- Lecellier CH, Dunoyer P, Arar K, Lehmann-Che J, Eyquem S, Himber C, Saib A, Voinnet O: **A cellular microRNA mediates antiviral defense in human cells.** *Science* 2005, **308**:557-560.
- Watanabe Y, Kishi A, Yachie N, Kanai A, Tomita M: **Computational analysis of microRNA-mediated antiviral defense in humans.** *FEBS Lett* 2007, **581**:4603-4610.
- Triboulet R, Mari B, Lin YL, Chable-Bessia C, Bennasser Y, Lebrignand K, Cardinaud B, Maurin T, Barbry P, Baillat V, Reynes J, Corbeau P, Jeang KT, Benkirane M: **Suppression of microRNA-silencing pathway by HIV-1 during virus replication.** *Science* 2007, **315**:1579-1582.
- Otsuka M, Jing Q, Georgel P, New L, Chen J, Mols J, Kang YJ, Jiang Z, Du X, Cook R, Das SC, Pattnaik AK, Beutler B, Han J: **Hypersusceptibility to vesicular stomatitis virus infection in Dicer1-deficient mice is due to impaired miR24 and miR93 expression.** *Immunity* 2007, **27**:123-134.
- Muller S, Imler JL: **Dicing with viruses: microRNAs as antiviral factors.** *Immunity* 2007, **27**:1-3.
- Skalsky RL, Samols MA, Plaisance KB, Boss IW, Riva A, Lopez MC, Baker HV, Renne R: **Kaposi's Sarcoma-associated Herpesvirus Encodes an Ortholog of miR-155.** *J Virol* 2007. [Epub ahead of print]
- Westerhout EM, ter BO, Berkhout B: **The virion-associated incoming HIV-1 RNA genome is not targeted by RNA interference.** *Retrovirology* 2006, **3**:57.
- Ding SW, Voinnet O: **Antiviral immunity directed by small RNAs.** *Cell* 2007, **130**:413-426.
- Bennasser Y, Le SY, Benkirane M, Jeang KT: **Evidence that HIV-1 encodes an siRNA and a suppressor of RNA silencing.** *Immunity* 2005, **22**:607-619.
- Haasnoot J, de VV, Geutjes EJ, Prins M, de HP, Berkhout B: **The Ebola virus VP30 protein is a suppressor of RNA silencing.** *PLoS Pathog* 2007, **3**:e86.
- Lin J, Cullen BR: **Analysis of the Interaction of Primate Retroviruses with the Human RNA Interference Machinery.** *J Virol* 2007. [Epub ahead of print]
- Rana TM, Jeang KT: **Biochemical and functional interactions between HIV-1 Tat protein and TAR RNA.** *Arch Biochem Biophys* 1999, **365**:175-185.
- Brady J, Kashanchi F: **Tat gets the "green" light on transcription initiation.** *Retrovirology* 2005, **2**:69.
- Karn J: **Tackling Tat.** *J Mol Biol* 1999, **293**:235-254.

47. Lu S, Cullen BR: **Adenovirus VAI noncoding RNA can inhibit small interfering RNA and MicroRNA biogenesis.** *J Virol* 2004, **78**:12868-12876.
48. Andersson MG, Haasnoot PC, Xu N, Berenjian S, Berkhout B, Akusjarvi G: **Suppression of RNA interference by adenovirus virus-associated RNA.** *J Virol* 2005, **79**:9556-9565.
49. Bennasser Y, Yeung ML, Jeang KT: **HIV-1 TAR RNA subverts RNA interference in transfected cells through sequestration of TAR RNA-binding protein, TRBP.** *J Biol Chem* 2006, **281**:27674-27678.
50. Cobb BS, Nesterova TB, Thompson E, Hertweck A, O'Connor E, Godwin J, Wilson CB, Brockdorff N, Fisher AG, Smale ST, Merken-schlager M: **T cell lineage choice and differentiation in the absence of the RNase III enzyme Dicer.** *J Exp Med* 2005, **201**:1367-1373.
51. Das AT, Brummelkamp TR, Westerhout EM, Vink M, Madiredjo M, Bernards R, Berkhout B: **Human immunodeficiency virus type 1 escapes from RNA interference-mediated inhibition.** *J Virol* 2004, **78**:2601-2605.
52. Westerhout EM, Ooms M, Vink M, Das AT, Berkhout B: **HIV-1 can escape from RNA interference by evolving an alternative structure in its RNA genome.** *Nucleic Acids Res* 2005, **33**:796-804.
53. Yeung ML, Bennasser Y, Myers TG, Jiang G, Benkirane M, Jeang KT: **Changes in microRNA expression profiles in HIV-1-transfected human cells.** *Retrovirology* 2005, **2**:81.
54. Chen D, Wang M, Zhou S, Zhou Q: **HIV-1 Tat targets microtu-bules to induce apoptosis, a process promoted by the pro-apoptotic Bcl-2 relative Bim.** *EMBO J* 2002, **21**:6801-6810.
55. Giacca M: **HIV-1 Tat, apoptosis and the mitochondria: a tubu-lin link?** *Retrovirology* 2005, **2**:7.
56. de MJ, Carre M, Barbier P, Campbell GR, Lancelot S, Opi S, Esquieu D, Watkins JD, Prevot C, Braguer D, Peyrot V, Loret EP: **HIV-1 Tat protein enhances microtubule polymerization.** *Retrovirology* 2005, **2**:5.
57. Satou Y, Yasunaga J, Yoshida M, Matsuoka M: **HTLV-I basic leucine zipper factor gene mRNA supports proliferation of adult T cell leukemia cells.** *Proc Natl Acad Sci U S A* 2006, **103**:720-725.
58. Cavanagh MH, Landry S, Audet B, rpin-Andre C, Hivin P, Pare ME, Thete J, Wattel E, Marriott SJ, Mesnard JM, Barbeau B: **HTLV-I anti-sense transcripts initiating in the 3'LTR are alternatively spliced and polyadenylated.** *Retrovirology* 2006, **3**:15.
59. Landry S, Halin M, Lefort S, Audet B, Vaquero C, Mesnard JM, Bar-beau B: **Detection, characterization and regulation of anti-sense transcripts in HIV-1.** *Retrovirology* 2007, **4**:71.
60. Ludwig LB, Ambrus JL Jr., Krawczyk KA, Sharma S, Brooks S, Hsiao CB, Schwartz SA: **Human Immunodeficiency Virus-Type 1 LTR DNA contains an intrinsic gene producing antisense RNA and protein products.** *Retrovirology* 2006, **3**:80.

Publish with **BioMed Central** and every scientist can read your work free of charge

"BioMed Central will be the most significant development for disseminating the results of biomedical research in our lifetime."

Sir Paul Nurse, Cancer Research UK

Your research papers will be:

- available free of charge to the entire biomedical community
- peer reviewed and published immediately upon acceptance
- cited in PubMed and archived on PubMed Central
- yours — you keep the copyright

Submit your manuscript here:
http://www.biomedcentral.com/info/publishing_adv.asp

